molecule encoding all or part of an HCV protein has been deleted, and wherein the HCV protein is selected from the group consisting of: p7, NS4B and NS5A proteins.

55. (Amended) A method of immunizing an animal against hepatitis C virus comprising administration of the pharmaceutical composition of claim 42, 48, 51 or 53 in an amount effective to induce immunity against hepatitis C virus.

56. (Amended) The method according to claim 55, wherein the pharmaceutical composition is provided prophylactically.

57. (Amended) The method according to claim 55, wherein the pharmaceutical composition is provided to an animal infected with a hepatitis C virus.

## REMARKS

Claims 42-57 are pending in this application. Claims 46-47 and 49-50 are withdrawn from consideration. Claims 44, 45, 48, 51-57 are rejected. Claims 44 and 54 have been cancelled.

Support for the amendments to the claims can be found throughout the specification, for example, at page 19, lines 12-16 and Examples 5-8. Applicants have attached a marked up version of the amended claims as Exhibit 1 showing all of the changes made to the claims relative to the previous version.

## Claim Objections

Claims 42, 48, 51 and 53 are objected to for informalities. Applicants submit that the amendments to the claims overcome the Examiner's objections.

## Double Patenting

Claims 42, 44-45, 48 and 51-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

1) claims 1-2, 9-11, 19-20 and 22 of U.S. Patent No. 6,153,421.

The Examiner contends that although the conflicting claims are not identical, they are not patentably distinct from each other because the "major difference between the instant claims and the claims of the '421 patent is the limitation of 'a suitable amount of a pharmaceutically acceptable diluent or excipient' in the claims of the instant application". The Examiner further argues that the limitation could encompass water in the purification and isolation of the nucleic acids recited in the claims of the '421 patent. Accordingly, the Examiner suggests to either amend the instant claims to recite "pharmaceutical compositions", or file a terminal disclaimer over the '421 patent.

In reply, Applicants submit that this rejection is rendered moot in view of the amendments to the claims. Applicants have amended the claims to recite "pharmaceutical compositions", as suggested by the Examiner. Therefore, Applicants respectfully request that the Examiner withdraw the double patenting rejection.

## Rejection of claims under 35 U.S.C. §102(b) and (e)

Claim 42 is rejected under 35 U.S.C. §102(b) as being anticipated by Yoo et al. (J. Virol., 1995, Vol. 69, No. 1, pages 32-38). According to the Examiner, Yoo et al. teach a synthetic RNA comprising the hepatitis C virus genome produced from a

transcription vector. The Examiner further argues that the RNA transcript was transfected into Huh7 cells and HCV was produced as evidenced by detection of HCV RNA and viral RNA replication as well as the presence of active HCV in the culture media (citing the Abstract).

In reply, Applicants respectfully disagree.

While Yoo et al. report that a full-length cDNA clone of HCV-1 was constructed, Figure 1 discloses that portions of the 3' region were *absent*. The 3' UTR of HCV consists of a short sequence of variable length and composition [variable region], a polypyrimidine tract [poly (U-UC) region] and a highly conserved sequence of approximately 100 nt at the 3' end. These three distinct regions have been found among isolates of all six HCV genotypes, including HCV-1, which is the isolate used by Yoo et al. The sequence of the conserved region has the potential to form three stem-loop structures including a highly stable stem-loop of 46 nucleotides at the 3' end.

Importantly, Applicants have shown herein that the 3' region is essential for infectivity *in vivo*. This was shown conclusively as disclosed on page 52, lines 4-14 and in Figures 17A - 17G, the construct pCV-H77C (-98X) containing a deletion of the 3'-most 98 nucleotide sequences of the 3'-UTR failed to replicate in chimpanzees. The chimpanzee is the only validated animal model for demonstrating infectivity and replication of HCV. Yoo et al fails to disclose any *in vivo* results from their HCV constructs. Applicants results demonstrate that a construct lacking the 3'-most 98 nucleotide sequence, as does the Yoo et al construct, is not infectious and not replication competent *in vivo*.

Further, Applicants attach as Exhibits 2-4, several more recently published reports which also demonstrate that the 3' UTR is required for infectivity *in vivo*. In Yanagi et al. (1999) (Exhibit 2) and Kolykhalov et al. (2000) (Exhibit 3), large sections of the 3' UTR were deleted from infectious cDNA clones of HCV and the RNA transcripts were tested for infectivity. Mutants lacking all or part of the 3'terminal conserved region (including each of the 3 stem-loop structures), or the poly U-UC region, were unable to infect chimpanzees, indicating that both regions are critical for infectivity *in vivo*. A deletion of the proximal 24 nucleotides of the variable region of the 3' UTR was viable in a chimpanzee and appeared to replicate as well as the parent virus. Overall, the poly U-UC region and the conserved region, but not the variable region, of the 3' UTR appear to be critical for *in vivo* infectivity of HCV. Thus, these recent results from studies in chimpanzees also disagree with the results in Yoo et al., and unambiguously demonstrate that the conclusions drawn in the earlier published *in vitro* studies, such as Yoo et al., are incorrect.

In addition, recent *in vitro* studies have shown that a subgenomic sequence of HCV, consisting of the 5' UTR, NS3-NS5B and the 3' UTR as part of a selectable bi-cistronic construct can function as a self-replicating unit in Huh-7 cells. Freibe et al. (2002) (Exhibit 4) report that mutational analysis of the 3' UTR in this system demonstrates that mutants with deletions of each of the stem-loop structures of the conserved region, or the entire conserved region, are completely incapable of replicating in Huh-7 cells. The Huh-7 cells are the same cells used by Yoo et al. Further, Friebe et al. found that the polypurimidine tract needed to be at least 26 nucleotides in length to permit replication. Tracts of G, A, or C did not replicate (the

clone in Yoo et al. has a poly-A tail at the 3'end). However, as with the *in vivo* results, mutants with deletions in the variable region could replicate *in vitro*.

Other researchers have confirmed and expanded on the results regarding the importance of the 3' UTR for *in vitro* replication (*see*, Yi and Lemon (2002) and Horscroft (2002) (Exhibit 5)). For example, Horscroft (2002) used HCV replicons to demonstrate that constructs such as Yoo et al.'s, lacking the 3'-UTR, also do not replicate *in vitro*. Thus, the data generated *in vitro* is consistent with *in vivo* results, and indicates that the constructs originally generated by Yoo et al. could not have been replication competent, and could not have produced viruses in cell culture.

Therefore, because Yoo et al. fail to teach or suggest the Applicants invention, Yoo et al. is not an anticipating reference under 35 U.S.C. §102. In view of this, reconsideration and withdrawal of the rejection of claim 42 under 35 U.S.C. §102(b) is respectfully requested.

Claim 42 is also rejected under 35 U.S.C. §102(e) as being anticipated by Houghton et al. U.S. Patent No. 5,679,342. The Examiner contends that Houghton et al teach a full length HCV RNA (R+HCVF) which was transcribed from a transcription vector. The Examiner further states that the RNA was transfected into Huh7 cells and active HCV particles were produced as detected by the presence of HCV RNA in the cells, viral RNA replication and infectious HCV particles in the culture supernatant. The Examiner also argues that Houghton et al teach that transfection of cells with HCV cDNA will also result in propagation of the virus.

In reply, Applicants submit that Houghton et al., as Yoo et al., fail to teach or suggest a 3'-most 98 nucleotide sequence of the 3'-UTR. Applicants submit that for the same reasons given above, the sequence taught by Houghton et al. would also fail to be infectious in vitro and in vivo. Therefore, the specific sequence recited in claim 42 is novel and patentably distinct over Houghton et al. Reconsideration and withdrawal of the rejection of claim 42 under 35 U.S.C. §102(e) is respectfully requested.

**Rejection of the Claims under 35 U.S.C. §112, first paragraph**

Claims 43, 55-57 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner argues that the claims drawn to methods of immunizing an animal against HCV using the nucleic acid compositions of the invention are not enabled due to the breadth of the claims, lack of guidance of the specification, insufficiency of working examples, and the amount of experimentation need.

In reply, Applicants submit that the Examiner's enablement rejection is rendered moot by the amendment to the claims, because the claims as amended are now drawn to HCV sequences SEQ ID NOs: 3 and 4. The present specification describes construction of expression vectors containing the HCV sequences of the invention (See, for example, page 16, lines 28-35). The specification also teaches use of the HCV proteins produced by the nucleic acid sequences of the invention as immunogens in live or killed vaccines to prevent hepatitis C in a mammal (See, for

example page 18, lines 12-16). The specification further teaches that the vaccines of the invention may be administered by a variety of routes, including intramuscularly (See, page 19, lines 17-21). The specification also teaches that the vaccines may be administered at doses ranging from about 100ng to 100ug (page 20, lines 1-3). Finally, Examples 5-10 of the specification describe in detail the isolation (Examples 5-6), construction of vectors (Example 7), and transfection of chimpanzees (Example 8) using the sequences recited in the claims. Based on the description in the specification, Applicants submit that one skilled in the art could readily practice the invention without undue experimentation.

As further evidence that the specification enables one skilled in the art to practice the invention, Applicants attach reports by Weiner et al. (2001) (Exhibit 6) and Bukh et al. (2001) (Exhibit 7) demonstrating the efficacy of genetic inoculation of HCV sequences (such as described in Example 8 of Applicants' specification) for stimulating protective immunity.

In view of the arguments and evidence presented above, Applicants respectfully request withdrawl of the §112, first paragraph rejection.

**Rejection of the Claims under 35 U.S.C. §112, second paragraph**

Claims 42-45, 48, 51-57 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner contends that claims 42, 48, 51, and 53 are vague and indefinite in that the "metes and bounds of the phrase 'suitable amount' does not appear to be clearly defined in the specification...".

Applicants submit that the amendments to claims deleting the phrase "suitable amount" overcome the Examiner's rejection. Therefore, Applicants request that the Examiner withdraw this rejection.

The Examiner also contends that claim 48 is vague and indefinite in that the metes and bounds of the phrase "wherein a fragment of said molecule which encodes the structural region of hepatitis C virus has been replaced by the structural region from the genome of another hepatitis virus strain" are unclear. According to the Examiner, the phrase is unclear in that it appears to specify that the nucleic acid sequence is replaced with a polypeptide sequence comprising the structural region of an HCV virus.

Applicants submit that the amendments to claim 48 overcome this rejection, as claim 48 recites that the nucleic acid fragment is "replaced with a portion of a nucleic acid molecule of a different hepatitis C virus strain that encodes the corresponding structural region". Therefore, Applicants request that the Examiner withdraw this rejection.

## AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account 13-4500, Order No. 2026-4276US1. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

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Dated: September 9, 2002

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## EXHIBIT 1

## MARKED UP VERSION OF AMENDED CLAIMS

42. (Twice amended) A pharmaceutical composition comprising a purified and isolated nucleic acid molecule [suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient], said nucleic acid molecule encod[es]ing a human hepatitis C virus having the amino acid sequence of SEQ ID NO: 3 [, wherein expression of said molecule in transfected cells results in production of virus when transfected into cells].

43. (Twice amended) A method for treating hepatitis C viral infection comprising the administration to an animal in need [thereof] of treatment a clinically effective amount of the composition of claim 42.

45. (Amended) The composition of claim 42, wherein the nucleic acid molecule comprises the [nucleic acid] sequence of SEQ ID NO:4 [shown in Figures 14A-14F].

48. (Amended) A pharmaceutical composition comprising a purified and isolated nucleic acid molecule [suspended in and a suitable amount of a pharmaceutically acceptable diluent or excipient], said nucleic acid molecule encod[es]ing a human hepatitis C virus having the sequence of SEQ ID NO: 3, [wherein transfection [expression] of said nucleic acid molecule into suitable [transfected] cells results in production of virus], and wherein a [fragment] portion of said nucleic acid molecule which encodes the structural region of hepatitis C virus has been replaced [by] with [the structural region from the genome of another] a portion of a nucleic acid

molecule of a different hepatitis C virus strain that encodes the corresponding structural region .

51. (Amended) A pharmaceutical composition comprising a purified and isolated nucleic acid molecule [suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient], said nucleic acid molecule encod[es]ing a human hepatitis C virus having the sequence of SEQ ID NO: 3,[ wherein expression of said molecule in transfected cells results in production of virus], and wherein a [fragment] portion of the nucleic acid molecule which encodes at least one HCV protein has been replaced [by] with a [fragment] portion of the genome of another hepatitis C virus strain which encodes the corresponding HCV protein.

52. (Amended) The composition of claim 51, wherein the HCV protein is selected from the group consisting of: NS3 protease, E1 protein, E2 protein and NS4 protein.

53. (Amended) A pharmaceutical composition comprising a purified and isolated nucleic acid molecule [suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient], said nucleic acid molecule encod[es]ing a human hepatitis C virus having the sequence of SEQ ID NO: 3, [wherein expression of said molecule in transfected cells results in production of virus], wherein a [fragment] portion of the molecule encoding all or part of an HCV protein has been deleted [and], and wherein the HCV protein is selected from the group consisting of: p7, NS4B and NS5A proteins.

55. (Amended) A method of immunizing an animal against hepatitis C virus comprising administration of [a] the pharmaceutical composition of claim 42, 48, 51 or 53 in an amount effective to induce immunity against hepatitis C virus.

56. (Amended) The method according to claim 55, wherein the pharmaceutical composition is provided prophylactically.

57. (Amended) The method according to claim 55, wherein the pharmaceutical composition is provided to an animal infected with a hepatitis C virus.